PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Staley A. Brod	Group Art Unit: 1647
Serial No.: 10/801,277	Examiner: Seharaseyon, Jegatheesan
Filed: March 16, 2004	Atty. Dkt. No.: CLFR:115USC1
For: Methods of Treating Rheumatoid Arthritis Using Orally Administered Type One Interferons	

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August 25, 2008
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David L. Parker

REPLY BRIEF

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REPLY BRIEF ON APPEAL

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Appellant hereby submits this Reply Brief on Appeal in response to the Examiner's Answer ("Ex. An."). The date for filing this Brief is on or before August 25, 2008. No fees are believed due in connection with the filing of this Reply Brief. Should any additional fees become due under 37 C.F.R. §§ 1.16 to 1.21 for any reason relating to the enclosed materials, or should an overpayment be made, the Commissioner is authorized to deduct or credit said fees from or to Fulbright & Jaworski Deposit Account No. 50-1212/CLFR:115USC1.

I. RELATED APPEALS, INTERFERENCES, AND JUDICIAL PROCEEDINGS

Appellant cited no related appeals, however, the Examiner has identified two (2) appeals asserted to be related to this appeal. Ex. An. at p.2. The Examiner identifies Appeal No. 2000-1094 (Application No. 08/946,710; parent of instant application) and Appeal No: 1999-2502 as related to the instant appeal, but contrary to the Examiner's assertion, Appeal No: 1999-2502 does not correspond to "Application No. 09/631,470." *Id.* Rather, it corresponds to Application No. 08/631,470, which is parent to 08/946,710.

Further, to the extent Appeal No. 1999-2502 and 2000-1094 may have any bearing on the instant appeal, Appellant also brings to the Board's attention Appeal No. 2008-2763 (Application No. 08/844,731; CIP of 08/631,470) which is on appeal and awaits a decision from the Board.

II. STATUS OF CLAIMS

All pending claims in the Application, *i.e.* claims 19-30, are under appeal. The claims on appeal are reproduced in Appendix A.

III. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

- **The Examiner states that the rejection of claims 19, 21-23, 25-27 and 29-30 for indefiniteness under 35 U.S.C. § 112 ¶2 has been withdrawn, however, claims 20, 24, and 28 remain rejected under 35 U.S.C. § 112 ¶2.**

- **Claims 19-22 remain rejected under 35 U.S.C. § 112 ¶1 for lack of enablement for prevention of destructive joint disease.**

- **Claims 19-26 remain rejected under 35 U.S.C. § 103(a) over Shiozawa *et al.* ("Shiozawa") in view of Cummins, U.S. Patent No. 4,497,795 ('795) and Cummins, U.S. Patent No. 5,019,382 ('382).**

- **Claims 27-30 remain rejected under 35 U.S.C. § 103(a) over Shiozawa in view of the '795 and '382 Patents and in further view of Aman *et al.* ("Aman").**

IV. ARGUMENT

A. 35 U.S.C. § 112 ¶2 ~ Indefiniteness

Now on appeal, for the first time, the Examiner apparently abandons a general indefiniteness rejection and states that, "claims 20, 24, and 28 lack antecedent basis for the disclosure of units." Compare, Ex. An. at p.10 with FOA 09/18/2007 at p.3 and OA 04/12/2007 at pp.3-4. If an Examiner identifies antecedent problems, the M.P.E.P. directs the Examiner to suggest corrections. M.P.E.P. §2173.05(e). This was never done in prosecution, or on appeal.

Additionally, the Examiner states for the first time that a person of skill in the art at the time the invention was made would believe "units" and "international units" in Appellant's claims, are different. Ex. An. at p.10. The Examiner looks to the teaching in the '382 and '795 Patents, to support this, stating those references, "discloses [sic] that 'unit' as disclosed means

the reciprocal of a dilution of interferon-containing material." *Id.* at p.9. Yet, the flaw in this argument is evident by the Examiner's own words: these patents limit the definition of that particular term to the context "***as disclosed***." The Patents themselves also make this clear, setting forth a meaning for the term "unit" specific only to the disclosure utilizing a qualitative test dependent upon the specific VSV virus. *See* '382 Patent at col. 3 ll. 45-52. Even the "conversion" the Examiner states is taught in the '382 Patent is only an approximation. *Id.* at col. 3 ll. 54-56 ("1 unit $\simeq$ 0.1 IU.").

Further, a person of skill would know that interferon units are now described as "International Units," in the art, but within the '795 Patent, units are internally defined by a qualitative method described in a 1967 journal article, and Example 1. '795 Patent at col. 4 ll. 59-68; Example 1.

> ***Interferon of human and murine origins has been quantified in the art in terms of International Units ("IU")***, notwithstanding knowledge that, for example, the molecular weight of human leukocyte and lymphoblastoid ranges between 13,000 and 25,000 daltons. ***As used herein, a "unit" of interferon shall mean the reciprocal of a dilution of interferon-containing material that, as determined by assay, inhibits one-half of a challenge virus plaque, the challenge virus being the vesicular stomatitis virus (VSV)***. Unless otherwise indicated, as used throughout the examples presented herein, "bovine fibroblast interferon, "bovine IFN," or "IFN" shall means that interferon which has been prepared in accord with the procedures of Example 1. ... The interferon activity (expressed as "units" as opposed to IU) ***was assayed by a plaque reduction method using VSV as a challenge virus on BFK cells*** Rosenquist and Loan, "Interferon Production With Strain SF-4 of Parainfluenza-3 Virus" Am. J. Vet. Res., 28, pp. 619-628 (1967).

Id. (emphasis added). Thus, contrary to the Examiner's assertion, the '795 and '382 Patents do not contradict Appellant's position and provide limited teaching.

Regarding the Examiner's indefiniteness rejection predicated upon the Examiner's suggestion that 30,000 units could refer to 30,000 units/kg or 30,000 units total dosage, the Examiner argues that, "there is no teaching in the instant specification with respect to the conversion of the units." Ex. An. at p. 10. Yet the flaw in this argument could not be more plain. The Examiner already stated that Appellant's position for purposes of the instant Specification is that "units" and "IU" are interchangeable. *Id.* at p.9. Thus, no conversion is required. As for comparing dosage by kilograms versus total dosage, that is a routine conversion well understood in the art. The Examiner's argument appears to deem the Appellant incorrect, but the Examiner fails to provide any law of facts to rebutt those Appellant has put forth. *Id.*

All that is required for definiteness is that the claims be amenable to construction. *Honeywell Int'l v. International Trade Comm.*, 341 F.3d 1332, 1338-39 (Fed. Cir. 2003). Here, the claims are definite and discernable when properly analyzed. M.P.E.P. § 2173.02. Appellant's chosen language complies with the statutory requirements of 35 U.S.C §112 ¶2, thus reversal of the rejection is respectfully requested.

B. 35 U.S.C. § 112 ¶1 ~ Enablement

The Examiner misstates the law governing enablement while arguing that Shiozawa and the instant Specification provide "sufficient, reasonable, specific ***or*** technical reasons to question enablement under 35 U.S.C. § 112." Ex. An at p.13 (emphasis added). Specifically, the Courts' rulings regarding enablement are not meant to be evaluated in the alternative. An Examiner making an enablement rejection must provide reasons (*i.e.* a basis) for questioning enablement, at a bare minimum. M.P.E.P § 2164.04; *In re Bowen*, 492 F.2d 859, 862-63 181 USPQ 48, 51

(CCPA 1974). Even when providing only the least explanation the rules allow, the Examiner's reason or basis must be ***sufficient and reasonable***. *Id.*; *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971) (emphasis added). The Patent Office must back up its assertions with acceptable evidence or reasoning. *Id.* "**[S]pecific, technical reasons** are always required." M.P.E.P § 2164.04 (emphasis added). Thus, the Examiner's burden is not discharged by providing "reasons," to question enablement unless they are sufficient, reasonable, specific, ***and*** technical.

Appellant also notes that the "Office takes no position" on Appellant's argument regarding the relevant law, but merely asserts Appellant's conclusions are incorrect. Ex. An. at p.12. Yet, the Examiner's arguments must be grounded in fact and law, just as Appellant's. *See* M.P.E.P. § Introduction ("In addition to the ***statutes*** and ***rules***, the actions taken by the examiner in the examination of applications for patents are to a great extent ***governed by decisions on prior cases***.") (emphasis added). An appropriate reply to Appellant's arguments per M.P.E.P. section 1207.02 responds to the contents of the Brief, and includes explanations for disagreement with Appellant's contentions. M.P.E.P. §1207.2.

The Examiner's rejection also appears to require enablement *per se*, which is not required under the law. M.P.E.P. §2164.02; ("An applicant need not have actually reduced the invention to practice prior to filing;" "The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it,") *Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987) quoting *In re Chilowsky*, 229 F.2d 457, 461, 108 USPQ 321, 325 (CCPA 1956)). Specifically, the Examiner states that the Specification,

> as filed is insufficient to enable one of skilled in the art to practice the claimed invention of preventing destructive joint disease associated with rheumatoid arthritis without an undue amount of experimentation because the specification and the prior art have not prevented destructive joint disease associated with rheumatoid arthritis by administering IFN-α orally.

Ex. An. at pp.4-5. Clearly, the Examiner is questioning enablement of the claims because Shiozawa and the working examples do not "prevent destructive joint disease." *Id.*

Further, when discussing Shiozawa as an indicator of lack of enablement, the Examiner offers inconsistent characterizations and unintelligible arguments. For example, the Examiner states that Shiozawa ***teaches*** treatment of destructive joint disease. Ex. An. at p. 11 (see below)

> disease. The prior art of Shiozawa also teaches the treatment and not the prevention of destructive joint disease.

Yet the Examiner concedes Shiowaza fails to ***mention*** destructive joint disease. Ex. An. at p. 13 (see below)

> The Office agrees with the Appellant that Shiozawa reference does not mention destructive joint disease. However, Shiozawa et al. reference was introduced to

Although not all RA sufferers will develop destructive joint disease (Specification, p.85 ll. 17-19), the Examiner argues Shiozawa treats destructive joint disease by treating RA. Ex. An at p.13. (see below)

> Although, Shiozawa does not explicitly treat destructive joint disease, the treating of rheumatoid arthritis will treat destructive joint disease associated with rheumatoid arthritis because it is treating the same patient population. It is also noted that the Office

It cannot be that the Examiner is attempting to show that Shiozawa's failure to prevent destructive joint disease renders the claims not enabled, because the Examiner admitted Shiozawa did not mention, let alone ***try*** to prevent, destructive joint disease. M.P.E.P. § 2164.06(b). Inherent treatment of destructive joint disease in Shiozawa, (which Appellant asserts is not taught) cannot impact enablement of Appellant's claims because inherency goes to obviousness, not enablement. M.P.E.P. § 2143.02. Appellant is at a complete loss as to what the Examiner is trying to convey regarding enablement. Whatever it is, it certainly cannot be a sufficient and reasonable basis, nor a specific and technical reason, to question whether Appellant's invention teaches prevention of destructive joint disease. The Examiner's burden is thus not met. M.P.E.P. § 2164.04 Appellant respectfully requests reversal of the rejection of claims 19-22 under 35 U.S.C. §112 ¶1.

C. 35 U.S.C. § 103 ~ Obviousness

The '795 Patent is clear. At the relevant time, it was widely believed that orally ingested interferon was not biologically active. '795 Patent, at col. 3 ll. 1-2. Appellant's approach defied this teaching. The '795 Patent further states that in humans, interferon causes nausea, fever,

increased white blood cell count, and appetite loss when administered to people. *Id.* at col. 3 ll. 32-38. The only application of ***oral interferon*** taught in the '795 Patent is to increase appetite in animals such as swine and cattle. *Id.* at Abstract; col. 3 ll. 51-54. Although the Examiner argues the '795 Patent was introduced to teach oral administration and dosage, (Ex. An. at p.22) these teachings are not made in a vacuum. They are specific to the disease, *i.e.*, appetite loss, which has nothing to do with Appellant's invention. No person of skill in the art would believe otherwise, as the correlation between dosage, form of administration, and activity is explicitly described. '795 Patent at col. 4 ll.5-19.

Regarding both the '795 and '382 Patents, Appellant has already thoroughly explained above and in the Appeal Brief that the conversions taught therein are relevant only to ***those*** particular inventions. Further, the '382 Patent limits dosage to 0.01-5 IU/lb per day. '382 Patent at col. 4 ll. 24-29. Taking note that 1 lb = 0.45359237 kg, that means that the '382 Patent teaches a maximum dose of 11 IU/kg interferon administered to the oral and/or pharyngeal mucosa of the patient by holding it in the mouth. *Id.* at col. 4 ll. 19-51. This is well below (nearly 5 times!) the dosage required in Appellant's invention and suggests an awkward form of administration that Appellant's claims exclude. Thus, the '382 Patent is also not applicable to Appellant's claims.

Additionally, the fact that references could theoretically be combined or modified does not, without more, render the resultant combination obvious. *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1396 (2007); M.P.E.P. §2143.01. These Patents would not be combined with Shiowaza because such a combination would render the prior art unsatisfactory for its intended purpose, or inoperable. *See* M.P.E.P. § 2143.01. No reason to

combine the references exists, then, unless a hindsight driven analysis that cherry-picks discrete portions of incompatible references, is employed, and such an approach is expressly prohibited. M.P.E.P. §§ 2141.02. (explaining that each prior art reference is viewed as a whole); 2142 (explaining hindsight is difficult to avoid, but is nonetheless prohibited).

The '795 Patent teaches oral administration of interferon would be inoperable if administered to Shiozawa's patients to treat RA, because the levels of interferon taught in the '795 Patent are taught as too low to have other therapeutic effects. '795 patent, at col. 3 ll. 50-54. Further, Shiozawa teaches patients exhibiting of side effects were excluded from the interferon study, but the '795 Patent teaches interferon causes fever and an increased white blood cell count. *Compare* Shiozawa p.405 *with* '795 Patent col. 3 ll. 32-38. Conversely, there is no reason a person of skill in the art would read the '795 Patent and believe oral administration of the described animal appetite stimulant could be applied to humans because the patent teaches that interferon has the ***opposite*** effect on humans. Thus, to the extent the '795 patent teachings might be extended to humans, a person of skill in the art would not believe appetite stimulation in humans would occur, and similarly to the extent that Shiozawa could be applied using oral interferon as the '795 Patent teaches, the resulting interferon levels would be too low for Shiozawa's purposes and/or cause significant side effects, thus rendering Shiozawa inoperable.

This is not a trivial ramification of combining the cited references; the M.P.E.P. is clear in stating, "The Proposed Modification Cannot Render The Prior Art Unsatisfactory For Its Intended Purpose." M.P.E.P. §2143.01. The Examiner argues that a suggestion to combine need not be express. Ex. An. at p.22. Yet, that is irrelevant in cases such as this, where the inoperability of the combination negates an asserted motivation. M.P.E.P. §2143.01.

Appellant also reiterates that Aman teaches that in monocytic cell culture, IFN-α ***does not suppress*** IL-1, but in stromal cell culture, IFN-α ***significantly suppresses*** IL-1 production. *See* Aman, p.4148 col. 1 ¶2. The Examiner argues that Aman as a whole teaches inhibition of cytokines, but notably, the Examiner utterly fails to address the section in Aman Appellant cites for the contradictory teachings. Ex. An. at p.23. The Examiner cites to the Abstract, and certain pages of Aman, but as to the relevant portion of Aman on page 4148, the Examiner apparently doesn't get that far. *Id.* In this case, Aman teaches both that IFN-α (1) greatly suppresses IL-1 and (2) entirely fails to suppress IL-1, depending on the cell culture receiving the interferon. Accordingly, the Aman reference essentially discredits itself. M.P.E.P. § 2143.01. No person of skill in the art would read Aman's description of a phenomenon reported in certain tissue cultures, but reported as absent in others, and believe one of those results, but not the other, would translate into a drug therapy for humans suffering from RA that swallow their treatment rather than having it directly applied. M.P.E.P. § 2143.02.

Regarding inherency, the Examiner offers an unintelligible statement on page 20:

> invention. Although, Appellant argues that this treatment not true they do not provide any evidence to contradict this position. The instant invention is drawn to preventing

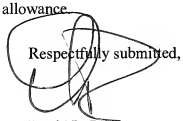
No meaningful reply could or should be expected. However, Appellant does note that Shiozawa does not teach a positive effect from interferon because Shiozawa patients took other disease modifying antirheumatic treatments ***during*** the interferon therapy, a limitation to the teaching that even Shiozawa noted. Shiozawa, p.407. The Examiner dismisses this deficiency as unimportant. Ex. An at p.21. Yet, Table I shows that the antirheumatic treatments were not consistent within or between groups of recipients of interferon, or the placebo. Shiozawa, at

Table I. Shiozawa simply ***cannot*** teach successful treatment of anything that could also be treated by any of these other drugs (*i.e.* rheumatic disease and inflammation), because it is too tenuous an assumption that interferon was responsible for the reported results.

Appellant has shown above that claims 19-26 are not obvious over the combination of Shiozawa in view of Cummins, '795 and Cummins '382; and claims 27-30 are not obvious over the combination of those references in further view of Aman. Reversal of the rejection of all claims under 35 U.S.C. § 103 is thus respectfully requested.

V. CONCLUSION

Appellant has shown above that all pending rejections are without merit and should be reversed. It is therefore respectfully requested that the Board overturn the rejections and recommend that this application proceed to allowance.



Respectfully submitted,

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Date: August 25, 2008

VI. CLAIMS APPENDIX

Appealed Claims:

19. A method of preventing destructive joint disease associated with rheumatoid arthritis in a human individual with an earlier stage of rheumatoid arthritis comprising: orally administering about 50 I.U./kg to about 25,000 I.U./kg of IFN-α to said individual; and immediately swallowing said IFN-α.

20. The method of claim 19, wherein about 30,000 units of IFN-α is orally administered.

21. The method of claim 19, wherein said IFN-α is administered every other day.

22. The method of claim 19, wherein said IFN-α is human recombinant interferon.

23. A method of reducing inflammation associated with rheumatoid arthritis in a human individual with rheumatoid arthritis comprising: orally administering about 50 I.U./kg to about 25,000 I.U./kg of IFN-α to said individual; and immediately swallowing said IFN-α.

24. The method of claim 23, wherein about 30,000 units of IFN-α is orally administered.

25. The method of claim 23, wherein said IFN-α is administered every other day.

26. The method of claim 23, wherein said IFN-α is human recombinant IFN-α.

27. A method of reducing a level of an interleukin in a human individual with rheumatoid arthritis, comprising: orally administering about 50 I.U./kg to about 25,000 I.U./kg of IFN-α to said individual; and immediately swallowing said IFN-α, thereby reducing the level of IL-1, IL-6, IL-8, or a combination thereof in said individual.

28. The method of claim 27, wherein about 30,000 units of IFN-α is orally administered.

29. The method of claim 27, wherein said IFN-α is administered every other day.

30. The method of claim 27, wherein said IFN-α is human recombinant IFN-α.

VII. RELATED PROCEEDINGS APPENDIX

Appellant brings to the Board's attention Appeal No. 2008-2763 (Application No. 08/844,731; CIP of 08/631,470) which awaits a decision from the Board